

WHAT IS CLAIMED IS:

1. A method of altering the degree of internalization of a Clostridial toxin into a cell, said method comprises the step of:
altering an activity of a lipid raft on a membrane of a cell, thereby altering the degree of internalization of the Clostridial toxin into the cell.
2. The method of claim 1, wherein the lipid rafts are caveolae.
3. The method of claim 1, wherein the lipid rafts are selected from the group consisting of caveolin-containing lipid rafts and non-caveolin-containing lipid rafts.
4. The method of claim 3, wherein the caveolin-containing lipid rafts contain a caveolin family member selected from the group consisting of caveolin-1alpha, caveolin-1beta, caveolin-2, caveolin-3, flotillin-1, flotillin-2 and combinations thereof.
5. The method of claim 4, wherein the caveolin family member is specifically expressed in a cell type selected from the group consisting of neuronal cells, astrocytes, glial cells, striated muscle cells, smooth muscle cells, cardiac cells, adipocytes, endothelial cells, secretory cells, type I pneumocytes, lung cells, kidney cells, dendritic cells, Mast cells, macrophages, T-cells, and B-cells.
6. The method of any of claims 1-5, wherein the activity lipid rafts is decreased by contacting the membrane of a cell with an activity inhibitor.
7. The method of claim 6, wherein the activity inhibitor comprises an antibody.
8. The method of claim 6, wherein the antibody is selected from the group consisting of humanized antibodies, polyclonal antibodies, monoclonal antibodies, and function blocking antibodies.
9. The method of claim 7, wherein the antibody is selected from the group consisting of

antibodies against caveolin-1alpha, caveolin-1beta, caveolin-2, caveolin-3, flotillin-1, flotillin-2, reggie-1, reggie-2, stomatin, VIP36, LAT/PAG, MAL, BENE, syntaxin-1, syntaxin-4, synapsin I, adducin, VAMP2, VAMP/synaptobrevin, synaptobrevin II, SNARE proteins, SNAP-25, SNAP-23, a membrane-associated Clostridial toxin receptor protein, synaptotagmin I, synaptotagmin II and GPI-anchored proteins.

10. The method of claim 7, wherein the antibody is selected from the group consisting of antibodies against GM1, GD1a, GD1b, GQ1b and GT1b.

11. The method of claim 1, wherein the activity is altered by changing the concentration of the lipid rafts.

12. The method of claim 11, wherein the activity of lipid rafts is decreased by contacting the membrane of a cell with a lipid raft concentration inhibitor.

13. The method of claim 12, wherein the lipid raft concentration inhibitor comprises a cholesterol-reducing agent.

14. The method of claim 13, wherein the cholesterol-reducing agent is selected from the group consisting of a statin, a cyclodextrin, a saponin, and a filipin.

15. The method of claim 12, wherein the lipid raft concentration inhibitor comprises a sphingolipid-reducing agent.

16. The method of claim 15, wherein the sphingolipid-reducing agent is a synthetic sphingolipid analogue.

17. The method of claim 15, wherein the sphingolipid-reducing agent is an inhibitor of sphingolipid synthesis.

18. The method of claim 17, wherein the inhibitor of sphingolipid synthesis is selected

from the group consisting of L-cycloserine, fumonisin B1, and D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol.

19. The method of any of claims 1-5, wherein the activity of lipid rafts is increased by contacting the membrane of a cell with a lipid raft activity enhancer.
20. The method of claim 19, wherein the activity enhancer comprises an antibody.
21. The method of claim 20, wherein the antibody links together (or causes colocalization or clustering of) components of lipid rafts.
22. The method of claim 19, wherein the activity enhancer comprises a lipid raft concentration enhancer.
23. The method of claim 22, wherein the lipid raft concentration enhancer comprises a cholesterol-enhancing agent.
24. The method of claim 23, wherein the cholesterol-enhancing agent is a synthetic cholesterol analogue.
25. The method of claim 22, wherein the lipid raft concentration enhancer comprises a sphingolipid-enhancing agent.
26. The method of claim 25, wherein the sphingolipid-enhancing agent is a synthetic sphingolipid analogue.
27. A method of preventing or treating botulinum intoxication in a mammal, said method comprises the step of administering a lipid raft activity inhibitor, thereby preventing or treating botulinum intoxication.
28. The method of claim 27, wherein the lipid raft activity inhibitor comprises an

antibody.

29. The method of claim 28, wherein the antibody is selected from the group consisting of humanized antibodies, polyclonal antibodies, monoclonal antibodies, and function blocking antibodies.

30. The method of claim 28, wherein the antibody is selected from the group consisting of antibodies against caveolin-1 alpha, caveolin-1 beta, caveolin-2, caveolin-3, flotillin-1, flotillin-2, reggie-1, reggie-2, stomatin, VIP36, LAT/PAG, MAL, BENE, syntaxin-1, syntaxin-4, synapsin I, adducin, VAMP2, VAMP/synaptobrevin, synaptobrevin II, SNARE proteins, SNAP-25, SNAP-23, a membrane-associated Clostridial toxin receptor protein, synaptotagmin I, synaptotagmin II and GPI-anchored proteins.

31. The method of claim 28, wherein the antibody is selected from the group consisting of antibodies against GM1, GD1a, GD1b, GQ1b and GT1b.

32. The method of claim 27, wherein the lipid raft activity inhibitor comprises a cholesterol-reducing agent.

33. The method of claim 32, wherein the cholesterol-reducing agent is selected from the group consisting of a statin, a cyclodextrin, a saponin, and a filipin.

34. The method of claim 27, wherein the lipid raft activity inhibitor comprises a sphingolipid-reducing agent.

35. The method of claim 34, wherein the sphingolipid-reducing agent is a synthetic sphingolipid analogue.

36. The method of claim 35, wherein the sphingolipid-reducing agent is an inhibitor of sphingolipid synthesis.

37. The method of claim 36, wherein the inhibitor of sphingolipid synthesis is selected from the group consisting of L-cycloserine, fumonisin B1, and D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol.

38. A method of preventing or treating a medical condition selected from a metabolic disorder, a muscular condition, a nervous system disorder and/or a pain condition in a mammal, said method comprises the step of administering a lipid raft activity enhancer, and administering a Clostridial toxin, thereby preventing or treating said metabolic disorder, muscular condition, nervous system disorder, pain and combinations thereof.

39. The method of claim 38, wherein said metabolic disorder is selected from the group consisting of diabetes, obesity and hypertension.

40. The method of claim 38, wherein said muscular condition is selected from the group consisting of muscular dystrophy, strabismus, blepharospasm, spasmodic torticollis, oromandibular dystonia, and spasmodic dysphonia.

41. The method of claim 38, wherein the nervous system disorder is an autonomic nervous system disorder.

42. The method of claim 41, wherein the autonomic nervous system disorder is selected from the group consisting of rhinorrhea, otitis media, excessive salivation, asthma, chronic obstructive pulmonary disease (COPD), excessive stomach acid secretion, spastic colitis, and excessive sweating.

43. The method of claim 38, wherein the pain condition is selected from the group consisting of migraine headaches, muscle spasm, vascular disturbances, angina, neuralgia, fibromyalgia, neuropathy, and pain associated with inflammation.

44. The method of claim 38, wherein the activity enhancer comprises an antibody.

45. The method of claim 44, wherein the antibody links together (or causes colocalization of) components of lipid rafts.
46. The method of claim 38, wherein the activity enhancer comprises a lipid raft concentration enhancer.
47. The method of claim 46, wherein the lipid raft concentration enhancer comprises a cholesterol-enhancing agent.
48. The method of claim 47, wherein the cholesterol-enhancing agent is a synthetic cholesterol analogue.
49. The method of claim 46, wherein the lipid raft concentration enhancer comprises a sphingolipid-enhancing agent.
50. The method of claim 49, wherein the sphingolipid-enhancing agent is a synthetic sphingolipid analogue.
51. The method of claim 38, wherein the lipid raft activity enhancer is a caveolae activator.
52. A method of inhibiting the formation of lipid rafts on a cell, said method comprising the step of contacting the cell with a Clostridial toxin, thereby inhibiting the formation of a lipid raft on a cell.
53. The method of claim 52, wherein the lipid rafts are caveolae.
54. The method of claim 52, wherein the lipid rafts are selected from the group consisting of caveolin-containing lipid rafts and non-caveolin-containing lipid rafts.
55. The method of claim 52, wherein the Clostridial toxin interacts with a caveolin family

member.

56. The method of claim 55, wherein the caveolin family member is specifically expressed in one or more cell types selected from the group consisting of neuronal cells, astrocytes, glial cells, striated muscle cells, smooth muscle cells, cardiac cells, adipocytes, endothelial cells, secretory cells, type I pneumocytes, lung cells, kidney cells, dendritic cells, Mast cells, macrophages, T-cells, and B-cells.

57. The method of claim 55 or claim 56, wherein the caveolin family member is selected from the group consisting of caveolin-1 alpha, caveolin-1 beta, caveolin-2, caveolin-3, flotillin-1, flotillin-2 and combinations thereof.

58. A method of treating a disease associated with lipid rafts, said method comprising the step of administering a Clostridial toxin.

59. The method of claim 58 wherein the disease is selected from the group consisting of hepatic insulin resistance, obesity, diabetes, hematopoietic condition, immunoinflammatory condition, and Alzheimer's disease.

60. A method of identifying a compound that alters internalization of a Clostridial toxin into a cell, said method comprises the steps of:

contacting a cell sensitive to Clostridial toxin with a test compound, and
screening for compounds that alter the affinity of the Clostridial toxin for lipid rafts.